REMARKS/ARGUMENTS

Claims 1, 3-5, 10-22, 25-40, and 78-80 are pending and stand substantively rejected. Claims 1, 20-22, 25, 27-30, 35, 37, 78, and 80 are presently amended. Claims 23, 24, 32, 33 are presently canceled. Reconsideration of the claims is respectfully requested.

Support for the amendments to claims 1, 78, and 80 can be found in the specification at, for example, page 61, line 1 to page 64, line 14. Claims 20-22, 25, 27-30, 35, and 37 are amended to conform antecedent basis with claim 1. Claim 37 is also amended to incorporate elements from independent claim 1. No new matter is introduced.

First Rejection Under 35 U.S.C. §112

Claims 1, 3-5, 10-22, 25-40, and 78-80 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. This rejection is traversed in part and overcome in part as follows.

The previous Office Action mailed December 5, 2005 indicated that certain *in vitro* methods are enabled by the specification. Subsequently, claim 79 was amended to recite an *in vitro* method. Applicants believe that the inclusion of claim 79 in the instant §112 rejection is a clerical error. If the Office Action intended to maintain the §112 rejection of the *in vitro* method of claim 79, clarification is respectfully requested.

First *in vivo* methods

The Office Action states that the specification is enabling for certain *in vivo* methods for reducing the size of a tumor. Amended claim 1 is drawn to such a method, and is therefore enabled.

Second *in vivo* methods

The Office Action states that the specification is enabling for certain *in vivo* methods for treating mammalian cancer cells. Amended claims 78 and 80 are drawn to such methods, and are therefore enabled.

Second Rejection Under 35 U.S.C. §112

Claims 20-22, 25-30, 35, and 37 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. This rejection is overcome in part as follows.

Amended claims 20-22, 25, 27-28, 30, 35, and 37 do not recite administration of protein. Claim 29 is canceled. Applicants believe claim 26 was inadvertently included in this rejection, as it does not recite administration of protein. Withdrawal of this rejection is respectfully requested.

Section 102 and/or Section 103

Claims 1, 3, 10, 18-22, 25-28, 31, 78-80 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by, or in the alternative under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 6,262,032 to Tocque ["Tocque"]. This rejection is traversed.

Tocque is not a §102(b) reference

To be anticipated under 35 U.S.C. §102(b), the claimed subject matter must be patented or described in a printed publication in the U.S. or a foreign country or in public use or on sale in the U.S., more than one year prior to the U.S. date of application.

The instant application claims priority to U.S. Provisional Patent Application No. 60/038,065, which was filed February 18, 1997. Tocque was patented July 17, 2001, which is not one year before the instant priority date. A corresponding Tocque PCT application was published June 25, 1996, which is also not more than one year before the instant priority date. Thus, Tocque is not available as a §102(b) reference against the pending claims. Withdrawal of this rejection is respectfully requested.

Tocque does not render the claims obvious

According to MPEP 2142, to establish a *prima facie* case of obviousness, (1) there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to the artisan, to modify the reference, (2) there must be a reasonable expectation of success, and (3) the cited reference must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the cited references, and not based on applicant's disclosure.

Amended independent claims 1, 78, 79, and 80 encompass methods for treating human head and neck, ovarian, prostate, and breast cell cells. Tocque describes a treatment of H460 lung cells, and contemplates the *potential* treatment of certain other adenocarcinomas (e.g. col. 4, lines 52-63).

No expectation of success

There is no indication in Tocque that the artisan would have a reasonable expectation of success for the presently claimed treatments. At best, in view of Tocque, the artisan might try the combination treatment on the other types of cells. However, this is not the standard of 35 U.S.C. § 103.

Cancer is a complex disease, involving a myriad of biological events. Because of this, different types of cancer drugs have different mechanisms of action. Different classes of cells react differently to different types of drugs. Combination therapy for cancer treatment can be complex in nature, and not all combinations can be predicted to work equally effectively. It is well known that different types of cancers have very different molecular basis for their pathology and therefore very different and unpredictable response to any given method of cancer therapy. It is not true that if a particular combination of agents could be used for treating one type of cancer cells (e.g. lung), then that particular combination could also be used to effectively treat other types of cancer cells (e.g. head and neck, ovarian, prostate, and breast).

Surprising results

Treatment of the presently claimed human cancer cells with p53 and a taxane is nonobvious because the combination exhibits surprising and unexpected results. It is well settled that non-obviousness can be established by a showing of evidence that the claimed invention yields surprising or unexpectedly improved properties. MPEP § 2144.08(II)(B). A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness, and may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989).

Unexpected results are demonstrated in Nielsen et al., "*Adenovirus-mediated p53 Gene Therapy and Paclitaxel Have Synergistic Efficacy in Models of Human Head and Neck, Ovarian, Prostate, and Breast Cancer*," Clin. Cancer Research 4:835-846 (1998). A copy is included with this Amendment. This study reports a synergistic effect of the combination of p53 and a taxane (e.g. paclitaxel) in four cell lines: human head and neck, ovarian, prostate, and

breast cancer cells (e.g. Table 1, p. 837). This is objective evidence that treatment with p53 and an anti-mitotic agent has a surprising and unexpected effect in these cells.

The record demonstrates that the substantially improved properties of treatment with p53 and a taxane are unexpected and would not have been obvious. In contrast, Tocque does not show a synergistic effect of p53 and a taxane, particularly not in the presently claimed cancer types. Therefore, the currently pending claims are not obvious in light of the general disclosure by Tocque. Absent a showing by the Office that the results shown in Nielsen et al. (1998) would have been expected by one of skill in the art, the rejection under § 103 must be withdrawn.

Second Rejection Under Section 103

Claims 1, 2, 10-13, 15-22, 25-28, 31, 34, and 78-80 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Tocque in view of U.S. Patent No. 5,932,210 to Gregory et al. ["Gregory"]. This rejection is traversed.

Applicants believe claim 2 was inadvertently included in this rejection, as it is canceled.

As noted above, there is no teaching or suggestion in Tocque that the artisan would have a reasonable expectation of success of treating head and neck, ovarian, prostate, and breast cancer cells with a nucleic acid sequence encoding a p53 tumor suppressor protein in combination with a taxane. Gregory has not been shown to remedy this deficiency. Withdrawal of this rejection is respectfully requested.

Third Rejection Under Section 103

Claims 1, 2, 10-22, 25-28, 31, 34, and 78-80 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Tocque in view Gregory. This rejection is traversed.

Applicants believe claim 2 was inadvertently included in this rejection, as it is canceled.

As noted above, there is no teaching or suggestion in Tocque that the artisan would have a reasonable expectation of success of treating head and neck, ovarian, prostate, and breast cancer cells with a nucleic acid sequence encoding a p53 tumor suppressor protein in

combination with a taxane. Gregory has not been shown to remedy this deficiency. Withdrawal of this rejection is respectfully requested.

Fourth Rejection Under Section 103

Claims 1, 3, 4, 10, 18-22, 25-28, 31, 35, 36, and 78-80 were rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 6,054,467 to Gjerset et al. ["Gjerset"]. This rejection is traversed.

Gjerset does not render the claims obvious

As noted above, a *prima facie* case of obviousness requires some suggestion or motivation to modify the reference, a reasonable expectation of success, and a teaching of all the claim elements.

Amended independent claims 1, 78, 79, and 80 encompass methods for treating human head and neck, ovarian, prostate, and breast cell cells. Gjerset describes a treatment of breast cancer cells with p53 adenovirus and cisplatin, and contemplates the *potential* treatment of certain other cancer cells (e.g. col. 3, lines 7-15) and the *potential* administration of certain DNA-damaging agents including paclitaxel and docetaxel (e.g. col. 2, line 66 to col. 3, line 6).

No expectation of success

There is no indication in Gjerset that the artisan would have a reasonable expectation of success for the presently claimed treatments. At best, in view of Gjerset, the artisan might try the combination treatment on the other types of cells. However, this is not the standard of 35 U.S.C. § 103.

As noted above, it is well known that different types of cancers have very different molecular basis for their pathology and therefore very different and unpredictable response to any given method of cancer therapy.

Surprising results

As noted above, the record demonstrates that the substantially improved properties of treatment with p53 and a taxane are unexpected and would not have been obvious. In contrast, Gjerset does not show a synergistic effect of p53 and a taxane, particularly not in the presently claimed cancer types. Therefore, the currently pending claims are not obvious in light of the general disclosure by Gjerset. Absent a showing by the Office that the results shown in

Nielsen et al. (1998) would have been expected by one of skill in the art, the rejection under § 103 must be withdrawn.

Allowable Subject Matter

No references were cited against claims 37-40. Claim 37 is presently amended to incorporate elements from amended claim 1, which Applicants believe is clear of any enablement issues. Hence, it is respectfully submitted that claims 37-40 are allowable.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,

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Attachment:

Nielsen et al., "*Adenovirus-mediated p53 Gene Therapy and Paclitaxel Have Synergistic Efficacy in Models of Human Head and Neck, Ovarian, Prostate, and Breast Cancer*," Clin. Cancer Research 4:835-846 (1998)

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